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The Management of Tetanus with Curare: Death from tetanus may result from spasm of the respiratory muscles, toxemia, pulmonary complications secondary to oversedation, or the cumulative effects of exhaustion, dehydration and inadequate nutrition. Tetanic contractions contribute importantly to the manifestations of the disease and, in the past, they have been treated usually by heavy sedation. The use of large amounts of sedatives is associated with a high incidence of pulmonary complications. Moreover, sedatives often fail to control tetanic seizures adequately. Curare, by blocking the transmission of the nerve impulse at the myoneural junction, reduces muscle spasm and results in marked muscular relaxation. Thus, it should be a valuable adjunct in the management of tetanic contractions. Curare has not been extensively employed in treating tetanus because the available preparations have varied greatly in potency and the response to a given dose has been unpredictable. In 1943 Cullen and Quion, using a highly purified preparation of curare, satisfactorily controlled tetanic seizures in one patient. Pure preparations, standardized by biological assay, are now commercially available. Two case reports demonstrate the use of curare by the authors in the management of tetanus and illustrate a dangerous complication induced by it in one instance.

Case 1. A 40-year-old laborer was admitted to Vanderbilt University Hospital, 7 January 1947, complaining of stiffness of the jaws and neck; 15 days previously he had crushed his right finger between two railroad ties. He refused tetanus antitoxin because on several previous occasions nausea, chills, and fever had followed its administration. The wound became infected but without lymphangitis or constitutional symptoms. He felt well until 3 days before admission when he awoke with slight stiffness of the neck and jaws. Increased muscular irritability developed gradually. Sudden noises or jarring caused generalized painful muscular contractions. These symptoms steadily increased in severity. Eighteen hours before admission he became unable to urinate.

Upon examination it was found that the patient's neck was stiff and trismus prevented opening of the mouth more than 1 or 2 cm. There was generalized muscular hyperirritability. Slight jarring of the bed caused painful muscular spasms and dyspnea. The tip of the right ring finger was lacerated and pus was exuding from beneath the nail. The abdomen was tense and the rectus muscles were spastic. All of the tendon reflexes were hyperactive. The white blood cell count was 19,000/cu. mm. with 73 percent segmented forms.

Following a negative intradermal skin test for hypersensitiveness to horse serum, the patient was given 45,000 units of tetanus antitoxin intramuscularly. Under sodium pentothal anesthesia the necrotic skin and the medial portion of the nail of the infected finger were cut away. Clostridium tetani was cultured from the debrided tissue. A filtrate of the culture of this organism produced convulsions in mice.

During the first 3 hospital days the patient remained moderately ill. The rectal temperature rose to 101.8° F. daily and there were frequent painful generalized muscular spasms accompanied by slight dyspnea. Catheterization of the bladder was necessary.

The first injection of 60 units of intocostrin was given on the morning of admission. It was followed immediately by marked subjective improvement and moderate muscular relaxation. Hyperirritability gradually returned and a second dose of 20 units was given after 1 and 1/2 hours. A total of 9 intravenous injections of intocostrin, ranging between 20 and 60 units each and averaging 40 units each, were given during the first 4 hospital days. Sodium phenobarbital was administered at frequent intervals; the patient also received several injections of codeine for the painful muscular contractions. Penicillin in doses of 30,000 units at intervals of 3 hours was administered for 17 days. The doses of curare which were employed in this case were not sufficient to control the muscular contractions completely throughout each 24-hour period. Nevertheless, the results obtained indicated conclusively that curare caused muscular relaxation and alleviated the painful spasms and that it was more effective than codeine in controlling pain. The subjective relief provided by it was more impressive than were the objective signs of improvement.

The patient made an uneventful recovery and was discharged 19 days after admission to the hospital.

Case 2. A 38-year-old caretaker was admitted to Vanderbilt University Hospital on 23 February 1947. On 16 February he had noted stiffness of the neck and jaws, slight trismus, and headache. He remained ambulatory until the day before admission when he experienced dysphagia, inability to open his mouth, generalized muscular stiffness and dyspnea. He had several painful tetanic seizures. There was no history of injury. He had never received tetanus toxoid or antitoxin. The patient was acutely ill and sweating profusely. Cyanosis was marked. The temperature was 100° and tachycardia was present. There was evidence of dehydration. There was marked opisthotonus, trismus, nuchal rigidity, and generalized muscular rigidity. The characteristic sardonic facies was present. Speech was not impaired. The respirations were labored and stridulous although movement of the thoracic cage was almost imperceptible. The abdomen was board-like and the lumbar muscles were in a completely rigid state. The jaws could be opened only 1/2 cm. All of the deep reflexes were hyperactive. Over the knuckle of the right index finger there was a superficial abrasion 1 cm. in length which was covered by a dry crust. The white cell count was 16,500, of which 86 percent were neutrophils. Lumbar puncture revealed normal cerebrospinal fluid. Cultures from the abrasion on the finger did not yield Clostridium tetani.

From the outset it was apparent that laryngeal spasm was severe and a factor in the production of the marked dyspnea and cyanosis. After sufficient intocostrin had been given to overcome the laryngeal and generalized muscle spasm (140 units in divided doses intravenously during a 4-hour period), it became necessary to hold the tongue forward. Otherwise, it fell back in the mouth and occluded the glottis. However, respiratory paralysis did not occur. At intervals oxygen was administered by mask. Initially, the accumulation of secretions in the pharynx proved troublesome. Atropine appeared to be helpful in its suppression.

Skin reactions to horse serum were negative; tetanus antitoxin in the amount of 40,000 units was administered intramuscularly. Penicillin in doses of 30,000 units intramuscularly every 3 hours was also given. Intocostrin was employed in doses of 40 units intramuscularly at 4-hour intervals with complete control of muscle spasms and trismus. Sodium phenobarbital, 0.24 Gm. daily, was administered. He was kept fairly comfortable on this therapeutic regimen and was able to take food by mouth and to void and defecate normally.

The patient slowly recovered. He was given 10,000 units of tetanus antitoxin daily for 4 days, during which time the temperature remained slightly elevated. Penicillin was discontinued on the 9th hospital day. The authors' supply of intocostrin became exhausted on the 9th day of treatment and for 16 hours none was administered. During this period nuchal rigidity and trismus reappeared and there were several mild muscular spasms. With the reinstitution of treatment with curare these symptoms promptly subsided. Intocostrin was discontinued on the 18th hospital day. The patient was then able to sit beside the bed and in a day or so became ambulatory on the ward. He had completely recovered when discharged from the hospital 34 days after the onset of the illness.

It is considered that these cases demonstrate that curare is effective in controlling the painful muscular contractions of tetanus. Whether or not treatment with this drug will lower the mortality rate in tetanus remains to be seen.

Curare, in blocking the transmission of the nerve impulse at the myoneural junction, causes inability of the curarized muscle cell to respond to acetylcholine. The release of acetylcholine by the neural impulse is not prevented by curare, but the response to this chemical mediator is blocked. This blocking is not due to a paralytic action of curare because the involved cells are still capable of responding to electrical and other chemical stimuli.

The chief danger in the use of curare in tetanus is the development of weakness or paralysis of the muscles of respiration following its administration. Therefore, constant attention during its use is mandatory. Neostigmine and physostigmine are physiological antagonists to curare and act immediately to relieve respiratory paralysis induced by it. One of these preparations should be kept by the bedside at all times while curare is being employed. Since these drugs increase bronchial secretions, atropine should be administered concomitantly. Artificial respiration may be lifesaving when respiratory paralysis

results from treatment with curare. It must be provided promptly and expertly until the curare antagonist, neostigmine, can be administered. (Am. J. M. Sc., April '48 - E. M. Ory and L. A. Grossman)

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Use of Intravenous Calcium Gluconate in the Relief of Pleuritic Pain: It is usually stated in textbooks of medicine and physiology that the pain of pleurisy is due to friction between the inflamed pleural surfaces. This is based partly on the demonstration by Capps and Coleman that the parietal pleura is sensitive to painful stimuli. Certain clinical observations on the relief of pleuritic pain by various methods have indicated, however, that the mechanism of the pain is more complex than simple friction between the pleural surfaces. The purpose of the present report is to describe the relief of acute pleuritic pain by the administration intravenously of calcium gluconate, and to discuss the significance of this and other observations in reference to the probable mechanism of the pain.

Thirty patients with acute pleuritic pain due either to pneumonia or pulmonary infarction were treated by the injection intravenously of from 10 to 20 ml. of 10-percent calcium gluconate during a period of from 2 to 4 minutes. The results are summarized in the accompanying table. Of the 3 patients who were unrelieved, 2 were likewise unaffected by procain block of the intercostal nerves and the third experienced relief from that procedure.

Diagnosis	Pneumonia	Pulmonary infarction
Complete relief	4	0
Partial relief	20	3
No relief	1*	2
Total patients	25	5

* This patient obtained no relief of pain with intercostal nerve block.

In only 4 of the 27 patients who obtained relief with calcium gluconate did the pain disappear completely and not return. Usually there was a very marked, but not complete relief; this was evidenced by easier, fuller respirations and ability to cough. The effect was evident within 60 seconds after beginning the injection. The residual pain was described by several patients as a dull ache unrelated to respiratory movements. When the pain relief was not permanent, there was gradual return after a period of from 30 to 60 minutes. Tenderness and hyperalgesia of the chest wall or upper abdominal muscles were also relieved by calcium only to reappear at the same time that the sharp pains on inspiration returned. In 10 patients, a second injection of calcium gluconate was again effective in ameliorating this pain. Most of the patients in this series were subsequently given more lasting relief by procain block of the intercostal nerves, or by ethyl chloride spray.

Two side-effects were noted: a sense of warmth and flushing, and occasional mild nausea. The drug was not used in patients receiving digitalis because of possible toxic reactions. In order to rule out the possibility that the sense of warmth and flushing after calcium played a part in the results obtained, several patients were first given 100 mg. of nicotinic acid intravenously. This caused marked flushing of the skin, but had no effect on the pain.

The practical value of the use of calcium injection lies in its simplicity. It enables the patient to cough and produce sputum, often of importance in determining the etiology of the pleurisy, and facilitates physical examination of the chest. Furthermore, as stated above, permanent relief of the pain occurs in some instances.

In 1940, Buchthal and Clemmesen demonstrated that various drugs, among them calcium salts, brought about relaxation of muscle spasm, evidenced both by palpable lessening of the spasm and by electromyographic changes. At the same time, pain was relieved. The fact that calcium injection has a definite effect in the restoration of normal muscle tone has been emphasized in other reports.

In 1928, Weiss and Davis obtained relief of pain in pleurisy by injection of procain into the skin at the site of pain and tenderness. Relief was immediate, often complete and permanent. Occasionally, after several hours, the pain returned and a second injection was necessary. They noted in several patients that relief of pain in one area resulted in its appearance at another site. This too could be relieved by intracutaneous injection of procain. They offered the suggestion that normal impulses from the skin play upon a focus in the spinal cord made irritable by increased afferent impulses from the pleura, and these are interpreted as pain.

In 1939, Schnur demonstrated that injection of procain directly into the pleural cavity at the site of maximum pain likewise afforded immediate and sometimes lasting relief.

Price in 1943 reported the use of procain block of the intercostal nerves in pleurisy. He inferred that relief was due to block of the fibers carrying pain, and pointed out that often only one procain block gave permanent relief of pain, despite the fact that the duration of effect of this drug could not be more than a few hours.

In 1944, Kelly pointed out similarities between chest pain associated with fibromyositis or muscular rheumatism and that accompanying the pleurisy of acute lung infections. Using the method of direct infiltration of the tender intercostal muscles with procain, he was able to obtain relief of pain in both types of disease. He concluded that the role played by abnormal sensitivity of the intercostal muscles in pleurisy was an important one, and perhaps of major significance in the causation of the pain.

Dybdahl in 1944 described the relief of pleuritic pain by the use of an ethyl chloride spray on the skin over the painful area. The authors also have been able to obtain striking relief with this procedure, many times complete and permanent. Although Dybdahl recommended that a series of concentric frozen wheals be made at the site of pain, it has been the authors' experience, as well as that of others employing the spray for other conditions, that actual freezing

of the skin is not necessary. The application of the spray for from 20 to 30 seconds, producing only a transient cutaneous anesthesia is often all that is required.

The use of ethyl chloride as a spray for relief of pain was first suggested by Kraus in 1935 as a rapid treatment of painful distortions of joints. In treating ankle sprains, one application of the spray may give lasting relief, if active motion of the joint is begun immediately and is continued for a time. Kraus suggested that momentary surface anesthesia in some way abolished painful muscle spasm and that continued active movement so restored the involved muscles to a normal or near normal state that spasm did not recur. Payr in 1934 had described the so-called "chain" effect of painful muscle spasm. The chain consisted of sensory nerve, spinal cord, motor nerve, muscle and sensory nerve. Pain originating anywhere in the course of this chain leads to painful muscle spasm and the pain of the spasm induces still more spasm and pain as the vicious cycle becomes established. If the chain can be broken at any point, the spasm is relieved and if the muscles can be restored to a more normal state during the pain-free interval (by active movement), the recurrence of spasm can be prevented.

That spasm of striated muscle can serve as a primary source of pain was shown by Kabat and Knapp who employed erythroidine for the relief of muscle spasm in acute anterior poliomyelitis. As spasm was relieved, pain disappeared. Wolff and his associates in their extensive studies on pain mechanisms have demonstrated that certain types of headache are due to spasm of the muscles of the scalp and neck. McClellan and Goodell pointed out the importance of abdominal muscle spasm in pain associated with disease of the urinary tract.

The relief of painful muscle spasm by curare has been demonstrated repeatedly. This drug seems to have a selective action on hypertonic muscles, relieving spasticity with little effect on muscles of normal tone. The authors have used curare in 2 patients suffering from severe pleuritic pain due to lobar pneumonia, and in both of them the pain was alleviated by this treatment.

The foregoing observations together with the results in this study with intravenous calcium gluconate seem to indicate that a major portion of the pain associated with pleuritis is due to a painful spasm of the intercostal muscles which perpetuates itself in a vicious cycle of spasm, pain, and more spasm. Relief by any method seems to depend upon interruption of this cycle at some point. (Am. J. M. Sc., April '48 - I. L. Bennett, Jr. and W. Lathem)

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Diethylacetamide in Shock: During the war the German workers Hecht and Weese, working at the I.G. Farben laboratories in Elberfeld, introduced as a blood substitute a substance formed by the polymerization of vinyl pyrrolidone. They showed that it could take the place of blood plasma, and it was

soon employed clinically. Various plasma substitutes which appeared to be of a similar kind, such as gelatin and pectin solutions, and isinglass, were studied in North America. All these were believed to act by their osmotic properties alone.

In 1946 Daniel Bovet and his colleagues, working at the Institut Pasteur, examined polyvinyl pyrrolidone for its value in traumatic shock. They chose to study this condition because they had previously investigated shock caused by histamine and its prevention by antihistamine substances such as neo-antergan. They produced shock in rats by the method of Noble and Collip, in which rats are placed in a drum which revolves in a vertical plane (the axis of the drum being horizontal), so that the rats fall to the bottom as the drum revolves. When rats are placed in the drum, their fate depends on the number of revolutions. The rats die in increasing percentage as the number of revolutions increases; 100 percent die after 800 revolutions. Bovet found that if the rats received an injection of polyvinyl pyrrolidone beforehand, given either subcutaneously or intraperitoneally in a dosage of 0.5 Gm. per kg. of body weight, then every rat survived 800 revolutions. The mortality was reduced even if the injection was made as long as 72 hours before the trauma. They tested the protective power of this substance against the toxin of Clostridium oedematiens and diphtheria toxin and found that whereas 32 control animals all died in two days after receiving Cl. oedematiens toxin (0.16 ml. per kg.), of 32 animals protected with polyvinyl pyrrolidone (0.35 Gm. per kg.), 15 survived for from 7 to 8 days.

The most interesting aspect of this investigation, however, came from Bovet's idea that the protective value of polyvinyl pyrrolidone might not lie in its physical properties but rather in its chemical composition. If the substance is split up, molecules of N-N-diethylacetamide are obtained, and, this very simple compound was found to give some protection. When 0.5 Gm. per kg. was given by intraperitoneal injection one hour before the rats were placed in the drum, 13 out of 40 animals survived, compared with only 1 of the 40 controls. The treated animals which died lived for a mean time of 11 hours, but the controls lived for only 3.5 hours. Other related substances were tested; some were active, some were not. Thus N-N-diethylpropionamide was effective, but not N-methylacetamide.

The discovery of simple chemical substances which counteract the effects of trauma, and presumably also of toxins, provides a new and more hopeful conception of the pathological changes occurring. (Annotation, Brit. M. J., 12 June '48)

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Use of Radioactive Diiodofluorescein in the Diagnosis and Localization of Brain Tumors: The use of fluorescein was recently suggested by the author,

working at the University of Minnesota Medical School, as an aid in the diagnosis of cancer. It was observed that brain tumors appeared to exhibit consistently a special affinity for the absorption of previously injected fluorescein.

In an attempt to extend the clinical usefulness of the fluorescein technic, radioactive derivatives of the dye have been prepared. Since it is considered safe for clinical purposes to use only those isotopes with a short half-life, and since the detection of deep-seated intracranial lesions requires the emission of gamma radiation, diiodofluorescein was synthesized to contain I^{131}. The amount of I^{131} added was adjusted to give 1 millicurie of radioactivity per 10 c.c. of a 2-percent solution of the final product, sodium diiodofluorescein. An amount of dye calculated to contain from 500 to 600 μc of radioactivity was injected intravenously in each case. In order to give a comparable dose of radioactivity to patients on subsequent days, increasing volumes of the dye were injected as the I^{131} decayed. Previous toxicity studies have shown that the ML/50 of diiodofluorescein is comparable to that of eosin; no toxic reactions have been encountered from the small amount of dye administered.

All counts were obtained by means of a beta-gamma Geiger-Müller tube protected from background radiation by a 2-cm-thick lead shield, provided with a lead cone to reduce the area being counted, and mounted on a portable x-ray unit. Thin lead foils were placed over the counter window to filter out beta radiation. A quenching circuit attached directly to the Geiger-Müller tube from the scaler allowed easy manipulation of the detection unit over the patient. Counts were taken for from 3- to 5-minute intervals at each of several positions on the skull with the cone of the detection unit directly on the skin. An attempt was made to obtain counts over symmetrical positions on the right and left sides of the head, as well as counts along the midline. After a complete survey, an examination of sites of higher activity was repeated in order to localize more definitely the suspected lesion. At times uncooperativeness of a patient due to the intracranial lesion made an adequate survey impossible.

Although counting was begun soon after dye was injected, differential readings between areas over the suspected tumor and symmetrical control areas did not become evident until an interval of from 2 to 4 hours had elapsed. This interval, required for the development of maximal differences in concentration of dye by the normal and tumor tissue, corresponds closely to the time lag prior to the appearance of maximal fluorescence noted in the earlier study of brain tumors. Soon after the dye is injected, higher counts are obtained over the large venous sinuses; then, as the dye is removed from the blood stream, the counts tend to equalize over all parts of the brain with the exception of the area over the tumor, where the highest counts are recorded. In cases in which the tumor is accompanied by a large amount of edema, somewhat higher counts may be obtained over the entire affected hemisphere. As experience with the technic increased, a single series of counts at the proper interval was found satisfactory to localize the tumor. A majority of the tests were carried out without knowledge of the neurological findings, roentgen examination, and staff

opinion. Only patients with questionable intracranial neoplasms were examined by this method.

To date 15 patients suspected of harboring intracranial neoplasms have been subjected to this technic. The last 12 cases are summarized in the table below. Three previous cases with known site of recurrence, following previous

		Clinical preoperative diagnosis	Conclusions from radioactive dye technique	Operative findings
(1)	K.W.	Meningeoma of right sphenoid ridge	No tumor	Aneurysm of right internal carotid
(2)	E.S.	(?)Tumor of right temporal or parietal lobe	Tumor of right parietal occipital area	Ependymal blastoma, right occipital lobe
(3)	T.B.	Tumor of right temporal lobe	(?)Tumor of right temporal area	Meningeoma of right middle fossa
(4)	P.K.	Metastatic tumor of right parietal lobe	Tumor in right parietal area	Metastatic tumor of right parietal lobe
(5)	L.S.	(?)Metastatic tumor of right motor cortex	No tumor on right; (?) tumor of left frontal lobe	No tumor on right, left side not explored
(6)	H.L.	(?)Tumor	Tumor of posterior frontal lobe on right	Glioblastoma of right temporal lobe
(7)	J.H.	Tumor of right frontal lobe	Tumor of right frontal lobe	Ependymal blastoma of right frontal lobe
(8)	J.B.	(?)Tumor	Tumor to left of the midline, posterior frontal area	Meningeoma of left posterior frontal area
(9)	G.H.	(?)Tumor	No tumor	Normal ventriculogram, no operation
(10)	E.J.	Large tumor of right parietal lobe	Tumor of right parietal area	Right parietal tumor by ventriculogram and biopsy
(11)	L.W.	Right acoustic neuroma	No significant counts	Right acoustic neuroma
(12)	A.B.	Subdural hematoma, right side	Tumor of right frontal lobe near midline	Meningeoma of right frontal lobe near midline

partial operative excision, were studied by the radioactive dye method before the diagnosis of new cases was attempted.

Correct diagnoses of negative findings (Cases 1 and 9), as well as positive, have been made. Case 12 is of special interest. From the results of the counts obtained with the radioactive dye technic, a definite area was outlined on the skull over the site of the tumor. This outline coincided closely with the extent of the superficially situated meningeoma found at operation.

The limitations of this technic are as yet unknown, and its clinical usefulness is still to be determined. Further studies of the differential concentration of the radioactive dye in normal and edematous brain tissue as well as various tumors, clinical and experimental, are in progress. Preliminary experiments utilizing induced brain tumors in mice have revealed the concentration of dye in the tumor tissue to be as high as 80 times that found in the adjacent normal brain. Measurements of various concentrations of radioactive diiodofluorescein under physical conditions simulating those found clinically have verified the feasibility of the technic and will be reported upon later. (Science, 28 May '48 - G. E. Moore)

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Brill's Disease: The name "Brill's disease" is usually given to the isolated cases of typhus fever that occur in the coastal towns of the northeastern United States. In 1934 Zinsser showed that these cases develop almost exclusively in immigrants from areas where there have been epidemics of louse-borne typhus fever. He demonstrated that the rickettsias that he was able to isolate from a few of these patients resembled the causative agent of epidemic or louse-borne typhus fever but that the disease was not associated with louse infestation. He came to the conclusion that Brill's disease represented a recrudescence of a latent infection of louse-borne typhus acquired while the patient had lived in an area where the disease occurred. Recently, Plotz has presented serologic studies on several cases in Jewish immigrants that support this concept.

In Zinsser's series of over 500 cases about 80 percent were in Russian-Jewish immigrants, whereas only 4 cases were reported in persons from Ireland. The diagnoses in most of Zinsser's cases were made on clinical grounds alone.

The authors present two cases of Brill's disease in Irish-born Americans who have lived in Boston for many years, with serologic evidence that their illness was due to an infection with the causative agent of epidemic or louse-borne typhus fever. These two cases are of additional interest because, until the appearance of the rash, the clinical findings were consistent with a diagnosis of primary atypical ("viral") pneumonia.

In both cases there was a prodromal period of 24 hours or less during which the patients complained of weakness and nausea. This was followed by a sudden onset of shaking chills and a rapid rise in temperature accompanied by the development of a severe, throbbing headache. On physical examination, both patients showed some inflammation of the pharynx and pulmonary signs consistent with a diagnosis of atypical (viral) pneumonia. This impression was strengthened by the low white-cell counts and by the findings in the x-ray films of the chest. A diagnosis of atypical pneumonia was generally accepted until the appearance of the rash, the character and distribution of which suggested the possibility of a rickettsial disease. Since the rash in Brill's disease is frequently absent or consists only of a few macules, the diagnosis might easily have been missed.

Negative results in complement-fixation tests for Rocky Mountain spotted fever in the first case and for Q fever, rickettsialpox, and psittacosis in the second case eliminated them as possible diagnoses. A rising titer of agglutinins for P. vulgaris (strain OX19) was considered to indicate a diagnosis of typhus fever. Endemic or murine typhus could not be ruled out in these cases on clinical or epidemiologic grounds. Epidemic or louse-borne typhus does not occur in this area because living conditions in general do not provide a louse-infested population, which is necessary for its spread and maintenance. Furthermore, if louse infestation were a factor, other cases from the same

home might be expected. Since both patients had been born in Ireland, where epidemic typhus has occurred, they were thought probably to have Brill's disease.

In both cases, the fact that the patients spent considerable time on the docks raised the question of possible infection from a shipboard source. This was particularly true of the first patient, who had been unloading cargo from Chile at about the time he became ill. Murine typhus was considered as a possible diagnosis, but the incubation period would then have been very short if the disease had been acquired from rats on this ship. However, on close questioning both patients were discovered to have come to the United States from County Galway, Ireland, where louse-borne typhus is known to occur. This area was the site of a serious epidemic in from 1903 to 1905, and an outbreak of over 134 cases occurred there as recently as 1942. The typhus epidemic of 1903 occurred when one patient was 13 and the other 7 years of age. Since typhus fever is often a mild disease in childhood, both patients could have been infected during this outbreak without an illness of such severity as to be readily remembered.

In both patients, the clinical course of the disease was consistent with that seen in Brill's disease. The low initial white-cell counts, which rose to 10,000 or more during the second week, are frequently observed in such cases. The development of thrombophlebitis as a complication in the second case was of particular interest since patients with typhus fever often develop thromboses of blood vessels.

The suspicion that these patients were having a recrudescence of a previous attack of louse-borne typhus fever was considered to be confirmed by serologic studies. The rickettsial complement-fixation tests gave consistently higher titers with the antigen of epidemic typhus rickettsia than with those obtained with the antigen of murine typhus rickettsia. This difference is considered to be diagnostic of epidemic typhus fever. Neither of these patients had received any typhus vaccines. It is considered that the high titer with the antigen of epidemic typhus was not due to the fact that these patients had had epidemic typhus fever as children with a marked rise in antibody titer for this antigen as an anamnestic reaction during an attack of murine typhus.

The diagnosis of Brill's disease should be considered in any foreign-born American, regardless of race, who comes from an area where epidemic typhus occurs and who suffers from an acute febrile illness characterized by severe headache, chills and fever with or without a skin rash. (New England J. Med., 17 June '48 - H. R. Morgan et al.)

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Effect of Benadryl Hydrochloride on the Tuberculin Reaction in Guinea Pigs: In this study, guinea pigs were used for an investigation of the possible

effect of an antihistamine agent on the tuberculin reaction produced by tuberculin, Tuberculin Old, Koch, and Purified Protein Derivative (PPD) prepared by the ammonium sulfate precipitation method of Seibert. Purified Protein Derivative first strength (0.00002 mg.) and 1:10,000 Old Tuberculin were considered suitable for threshhold levels. Two higher concentrations of each tuberculin were also used. Although there is some disagreement concerning the mechanics and classification of the various phases of tuberculo-immunity, the author believes that specific tuberculo-allergy as manifested by the tuberculin skin reaction is a distinct entity.

The guinea pigs used in the study were healthy, white, and of from 350 to 400 Gm. weight. They were given intraperitoneally a suspension of mixed human and bovine strains of M. tuberculosis following a predetermined dosage plan that has been employed repeatedly to induce tuberculin sensitivity.

The results obtained clearly indicate that benadryl protected the skin from developing a tuberculin reaction in 50 percent of the guinea pigs from 0.00002 mg. of tuberculin PPD in 24 hours and in 23.3 percent of the guinea pigs from 1:10,000 Tuberculin Old, Koch, in 24 hours. When a large dose of Tuberculin Old, Koch, was given (1:10 dilution), considerable necrosis was encountered. With the use of benadryl, there was a lessening of the necrotic effect in all guinea pigs on retesting, and in 78 percent of the animals necrosis was suppressed up to the end of a 48-hour observation period.

Because most tuberculin testing of both adults and children is started at the so-called threshhold levels of tuberculin (0.00002 mg. of tuberculin, Purified Protein Derivative or 1:10,000 Old Tuberculin) in order to reduce the possibility of severe reactions, it is important to determine whether the individual being tested is receiving any antihistamine compound at the time of tuberculin testing before correct interpretation of a negative reading can safely be made. (Am. Rev. Tuberc., May '48 - R. W. Sarber)

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The Use of Benadryl in Paralysis Agitans: Paralysis agitans (Parkinson's disease) is a chronic progressive disease of the corpus striatum and extrapyramidal motor system for which there is no known cure. Treatment has always been symptomatic, and the drugs found to be useful have been limited almost entirely to hyoscine, hyoscyamine, belladonna, and stramonium, either individually or in various combinations. Amphetamine sulfate (benzedrine) has occasionally been beneficial in relieving some of the symptoms, but its mechanism of action has never been clearly explained.

The use of benadryl in paralysis agitans was first tried on a patient in September, 1946, on a purely empirical basis. The result was so gratifying that other subjects with paralysis agitans were also given the drug to determine

whether the improvement noted in the first patient was simply an unusual response in a suggestive person or whether the reaction could be consistently reproduced in others. There is no literature on the use of benadryl in paralysis agitans, but McGavack, Elias, and Boyd mentioned its use in 4 patients, with improvement in 3.

Eight patients suffering from paralysis agitans, all of them in the arteriosclerotic group, were treated with benadryl over a period varying from 3 to 14 months. All patients noted considerable improvement in the symptoms as long as the drug was administered. Four of the treated patients continued to use parasympathetic-inhibitory drugs of the atropine series, and there seemed to be a synergistic action between these drugs and benadryl.

The benefits derived from the use of benadryl in these patients can hardly be considered due to the enthusiasm with which a new drug is often received. However, the good results obtained in this small group may not withstand the test of larger series of cases.

The beneficial results are not readily explained. An atropine-like action of the drug has been described, and its effect in paralysis agitans may be similar to that of atropine. Furthermore, congestion of the choroid plexus has been observed in animals intoxicated with benadryl. This effect may produce an enhancement of the circulation of the corpus striatum, in which the symptoms of paralysis agitans are initiated. Pyribenzamine, an antihistamine drug closely related to benadryl, apparently was ineffective in the treatment of paralysis agitans.

Benadryl (administered alone or in conjunction with atropine-like drugs) is suggested as an added therapeutic agent in paralysis agitans.

Since this paper was submitted for publication 2 additional patients with paralysis agitans have been treated with benadryl. The response to the drug was excellent in both cases. (New England J. Med., 17 June '48 - J. Budnitz)

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Folic Acid and Pernicious Anemia: Folic acid (pteroylglutamic acid) was heralded in 1946 as one of the "wonder drugs" of the year. A few mg. of the drug given orally was often found sufficient to cause a dramatic remission in typical cases of pernicious anemia. In such related conditions as sprue, pernicious anemia of pregnancy, and tropical macrocytic anemia, the drug seemed to have an even greater therapeutic effect than did liver extract.

The physiologic mechanisms by which folic acid is effective are still quite obscure, but there can be no doubt that the various studies which have followed its introduction have illuminated certain aspects of the pathogenic mechanisms

in pernicious anemia. During 1947 it became apparent that folic acid often failed to prevent the development or progression of neurologic symptoms and that the signs of spinal cord involvement might develop explosively in patients taking the drug.

Towards the end of 1947 an editorial entitled, "A Warning Regarding the Use of Folic Acid," appeared in the New England Journal of Medicine (see News Letter of 21 Nov. '47) which not only cast doubt on the ability of folic acid to prevent neurologic involvement but even raised the possibility that the material might have a more or less directly harmful effect on central nervous system tissue. So striking has been the impact of this editorial that many physicians have discontinued completely the use of folic acid in their practice.

The warning editorial stemmed in part from the work of Ross and his collaborators. Some observations had already been made indicating that both the naturally occurring l(+) and d(-) glutamic acid are involved in nerve tissue metabolism. Glutamic acid is one of the constituents of the folic acid molecule, and Ross points out that its position in the molecule suggests that it may enter into competition with the naturally occurring l(+) glutamic acid and thus interfere with normal nerve metabolism. Ross implies that this interference might explain the greater frequency of neurologic relapse in patients receiving large doses of folic acid and the progression of neurologic disease in others.

From the available evidence, it appears probable that folic acid cannot be relied upon as the sole agent in the treatment of pernicious anemia, since its use not only may not prevent injury to the central nervous system but may actually be attended with harmful effects to nerve tissue. Liver extract must, therefore, remain, at least for the present, the sheet anchor in the treatment of Addisonian pernicious anemia. This does not exclude the possibility that folic acid may also be useful (1) as an adjuvant to liver extract therapy and (2) as a more specific substance than liver extract in certain conditions related to Addisonian pernicious anemia but not identical with it.

As regards the first possibility, Meyer, for example, holds to the opinion that small doses of folic acid, combined with liver extract injections, induce better remissions, both hematologic and neurologic, than either substance alone. Ross et al. also state: "These observations suggest that a combination of orally administered folic acid and parenterally injected liver extract may maintain a better hematologic status than either substance alone." In the author's experience, small doses of folic acid, e.g., 5 mg. per day, have proved useful in the maintenance therapy of pernicious anemia, in conjunction with injections of liver extract at from 2- to 4-week intervals. This combination has seemed desirable on physiologic grounds since (1) an active therapeutic agent is given daily to supply a chronic deficiency state and (2) the patient receives at stated periods a deposit of a known and time-tested material, i.e., liver extract. Under this regimen, all the patients treated have stated that their feeling of vitality is considerably improved; in addition, their red cell counts

have tended to be higher than on liver extract alone. No evidence of neurologic relapse has occurred. It is believed that folic acid is of distinct value as an adjuvant to liver extract therapy.

In 2 of the author's cases of pernicious anemia with neurologic manifestations, the administration of folic acid was followed by a distinct neurologic remission after prolonged liver extract therapy had proved ineffective. In one of these cases, a reticulocytosis of 8.2 percent developed at a red cell level of approximately 4.0 million cells per cu. mm., whereas previously, liver extract therapy had resulted in only a 2.4 percent response at a level of 3.8 million cells. These findings seem to indicate that at least for these particular patients, folic acid was more nearly the required specific substance than was liver extract.

In conditions such as sprue, the macrocytic anemia of pregnancy, the so-called tropical macrocytic anemia, and the megaloblastic macrocytic anemia of infancy, the efficacy of liver extract, particularly of the refined type, leaves much to be desired. Lucy Wills, for example, writes that "the liver principle is actively curative in pernicious anemia but does not seem to be the missing factor in nutritional macrocytic anemia. . ." This "missing factor" was alluded to by Watson and Castle as the "Wills' factor" in an article dealing with the therapeutic inefficiency of parenteral liver extract in certain cases of atypical pernicious anemia. It is possible that the missing factor is folic acid, especially since various workers have demonstrated that this material often results in a more marked therapeutic effect than does liver extract in cases of atypical pernicious anemia. Results in these cases suggest that the chemical acts specifically on certain enzyme systems that are not appreciably affected by liver extract. They also indicate that there may be different types of pernicious anemia brought about by varying mechanisms and even by different deficiencies.

The exact place of folic acid therapy still remains to be clearly defined. That it is harmful to central nervous system tissue has not been conclusively demonstrated. Certainly the evidence at hand hardly justifies the categorical statements that the drug "should not be used in the treatment of pernicious anemia" and other nutritional macrocytic anemias and that its use appears to offer "only risk to the patient." These gloomy forebodings are hardly borne out by the results of many workers, particularly in the field of atypical pernicious anemia. Suarez, for example, states that in the treatment of over 100 cases of sprue, not only has he seen no evidence of harm neurologically but the patients do better than with liver extract. Spies and co-workers have recently shown that patients with nutritional macrocytic anemia can be maintained for as long as two years with folic acid as the sole medication without the development of subacute combined degeneration of the spinal cord. When more is known about the specific enzyme systems concerned in the mechanisms of pernicious anemia, the rightful place of folic acid in the treatment of certain aspects of the pernicious anemia "family" of deficiency diseases should be found. (Editorial, Blood, J. Hematol., June '48 - W. Dameshek)

The Spread of Q Fever: Q, or Queensland fever, was first described by Derrick in Australia in 1937, and the causal agent was subsequently shown to be a rickettsia by Burnet and Freeman. Almost at the same time the disease was found to be occurring in Montana in the U.S.A. Spontaneous infections were most common among those concerned with cattle, alive or dead. Thus stockmen and those working in slaughterhouses were most commonly affected (see News Letter of 27 Feb. '48, p. 22). It was discovered that the causal agent, Rickettsia burneti, was carried by various cattle ticks - in Australia by Haemaphysalis humerosa (see News Letter of 30 Aug. '46, p. 13), and in the United States by Dermacentor andersoni, D. occidentalis, and Amblyomma americanum. In Australia the common bandicoot also appeared to act as a carrier.

During the latter part of 1944 and in the following war years there were outbreaks among British, New Zealand, and American troops in Greece and Italy of what was at first taken to be atypical pneumonia (see News Letter of 10 May '46, p. 7). By the use of complement-fixation tests these outbreaks have since been shown to have been due to Q fever. In Morocco, Blanc et al. have isolated the rickettsiae of Q fever from ticks, Hyalomma savignyi, H. dromedarii, and H. excavatum var. lusitanicum, found living on camels or in the burrows of a small North African rodent, the merion, Meriones shawi; moreover the rickettsiae of Q fever have been isolated from the spleens of apparently healthy merions. In addition, goats and camels in the same area carry infected ticks, and when inoculated with R. burneti goats, sheep, camels, and cattle suffer from a febrile illness during which rickettsiae circulate in the blood. There have been further reports of the disease from Texas in the U.S.A., and from Central America, where Panama is an endemic zone. A further extension of the range of Q fever has now been reported by Gsell, who has described four small familial outbreaks in Switzerland. In the epidemics affecting troops in Italy and Greece as well as in these Swiss outbreaks the role of ticks appears uncertain.

In 1940 Findlay showed that infection could be transmitted intranasally to mice, with the production of characteristic lung lesions. It is probable that the nasal mucosa or the conjunctival sac was the portal of entry in the numerous laboratory infections which have since occurred. In the National Institute of Health of the U.S.A. for instance, an outbreak began among laboratory workers in February, 1946, and by the end of May, 1947, there had been 47 cases.

The incubation period of Q fever is from 12 to 23 days. There are at first vague prodromal symptoms, headache, malaise, and general aching, usually for not more than from 12 to 24 hours. These symptoms are followed by severe headache, so characteristic of all rickettsial and many virus infections, and sometimes stiffness of the neck. Fever lasts on an average about six days, though some patients may have only one day and others fifteen days of high fever, occasionally up to 106° F. (41.1° C.). Rigors and sweats are not uncommon, and generalized aching in the limbs is very frequent. Aching may continue into convalescence. Nausea, vomiting, abdominal pain, diarrhea, or constipation are common symptoms, and in nearly a third of the cases there

is clinical or radiological evidence of pneumonitis, occasionally with blood in the sputum. No significant or consistent changes are found in the blood picture. A macular rash has very occasionally been seen. It is obvious that the signs and symptoms are such as may be present in many virus and rickettsial infections.

During the acute stage Rickettsia burneti is present in the blood and sputum, and by inoculation into mice or guinea-pigs the rickettsiae can be isolated. They are present in the spleen of experimental animals in considerable numbers. During convalescence the best method of diagnosis is by complement fixation, since complement-fixing antibodies are present from 10 to 15 days after the onset of illness.

The administration of neither penicillin, sulfonamides, nor of immune serum has any marked action in shortening the disease. Para-aminobenzoic acid (PABA) therapy has not yet been tested, but there is now evidence from the experiments of Huebner et al. that streptomycin has a curative effect not only when R. burneti is injected into the developing chick embryo but in guinea-pigs given large intraperitoneal injections of the organisms. When doses of 30 mg. of the drug were injected subcutaneously from 3 to 6 times a day there was very prompt disappearance of symptoms. Treatment was continued for from 12 to 16 days. (Annotation, Brit. M. J., 12 June '48)

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Studies on the Use of DDT and Phenyl Cellosolve for Control of Pediculosis

These studies were directed toward control of epidemic typhus and other diseases transmitted by lice by suppression of the vector with the insecticides DDT (2, 2-bis (p-chlorophenyl) 1, 1, 1-trichloroethane) and phenyl cellosolve (beta-hydroxyethyl phenyl ether). The effectiveness of DDT as a delousing agent has been conclusively demonstrated and results of similar studies in Mexico and other countries indicated the desirability of determining whether its use either alone or in combination with phenyl cellosolve would provide a simple, inexpensive, yet effective, procedure of delousing entire populations under conditions obtaining in small highland communities in Colombia in which the disease is endemic. If so, its use could be adopted as a routine measure for control of epidemic typhus in isolated rural villages of low cultural and economic standards. This study forms part of a more inclusive long-range one, as yet unreported, in which an attempt was made to determine the relative effectiveness and cost of mass delousing as against vaccination in the control of epidemic typhus fever as it occurs in Colombia.

The communities of Imues and Yacuanquer in the Department of Nariño were selected for study because typhus has been endemic in them for a long time, because of the high louse-infestation index as well as the stability of their populations, and because of their relative accessibility from Pasto and Ipiales in which are located two important health centers of the region.

Moreover, they are fairly representative of the highland villages of Colombia and of most of those located in "La Sierra" or highlands of the western Andes of South America.

The objective in Imues was to determine the minimum frequency of application of DDT and phenyl cellosolve lotion necessary to maintain the louse-infestation index at a level sufficiently low to render unlikely the transmission of louse-borne typhus fever on a significant scale, and simultaneously to determine factors which tend to lower the cost and increase the effectiveness of the procedure.

The purpose in Yacuanquer was to determine the time interval necessary for the louse-infestation rate to reach its original level following one application of the insecticides to all or a high proportion of the population.

Two weeks before the application of the insecticides a complete census was made of the populations and buildings, sketch maps of the towns were prepared, and the streets and houses were numbered. Details and the objectives of the program were explained to the ecclesiastic and civil authorities in order to secure their cooperation and assistance. The great benefits that could be expected from the application of the delousing agents were emphasized. While the census was being taken a health education campaign was carried out, principally by friendly personal explanations of the ease and harmlessness of the treatment and of its advantages. Educational pamphlets were also distributed. Moreover, public announcements by the clergy and by the civil authorities contributed materially to a satisfactory response from the people. Small bars of soap and combs, as well as some linens and clothing, were also distributed to the poorest inhabitants in order to assist further in arousing public collaboration. Free medical assistance and drugs were also given to the sick.

After these preliminary steps, the DDT and lotion were applied from house to house. The insecticides were applied to all individuals contacted, to reserve clothing, to beds, mattresses, and bedclothing. Special attention was paid to inner garments and "follados" (a kind of underskirt) which offer good harborage to the insect. Special efforts were made so that housewives would permit the treatment of all clothing, linen, etc., stored in the house.

The lotion was applied in the form of a shampoo, care being taken to wet all the hair, with emphasis on the temporal and occipital regions. The people were advised to close their eyes during the application to avoid irritation from the liquid. After a light massage the hair was combed with a fine-toothed horn comb.

The personnel worked until late in the evening in order to treat laborers who were home only at night. For those who were missed at the initial visit word was left to expect a follow-up visit or to present themselves at the local

treatment center. Experience showed, however, that it was necessary for an inspector to be available on the Sunday following the initial application to treat persons who came to the market only on that date and those who worked from early morning to late in the night.

Hand dusters were used exclusively in applying DDT-10 to individuals and were found to be particularly suitable. The dusting was rapid and complete and it was not necessary for the subjects to undress, an important detail when dealing with women. When the dusters are properly handled, powdering of both inner and outer garments is quite satisfactory.

Sifter-top cans were sometimes used for the dusting of beds, bedding and excess clothing, with less wastage of DDT than when dusters were used, but the dusters permitted more rapid operation.

One physician, 3 sanitary inspectors and 3 local nurses were engaged in the work. Three teams, consisting of a sanitary inspector and a nurse, were each assigned to treat one-third of the community. The physician directed the work and had control of the teams, and in addition gave free medical assistance to all patients who desired his services. This latter feature contributed materially to the success of the project and is considered indispensable in work of this nature.

Detailed instructions were given to the personnel regarding the handling of the equipment, the way in which the insecticides should be applied to individuals and to beds and stored clothes, the health education campaign to be carried on, and how to approach the people. The program was thoroughly explained to them in order that they, in turn, could answer any questions asked by the public, and also so that they would appreciate their responsibility for its successful execution.

It was considered desirable and less expensive to employ local instead of professional nurses, despite their deficiencies in training, in order to avoid transportation difficulties, to have nurses available for longer working hours, and particularly for their influence in gaining the confidence of the population.

In the dusting operations the nurses were useful mainly in persuading the women to allow themselves to be treated and to present for dusting all clothing not in use. This latter point is important because it was found that there was a reluctance to show ragged or badly worn clothing.

The inspectors did all the dusting and kept records of louse infestation and all other pertinent data on especially prepared forms.

In these studies no attempt was made to evaluate the degree of louse infestation in an individual, but to determine only whether viable eggs or adults of both head and body lice were present or absent. In the examination of men for body lice the inside seams and faces of the collars of the shirt and coat were first

examined carefully, and if lice or eggs were not present the interior seams of the shirt and undershirt near the belt line were next examined. If still negative, examination was made of the seams and interior surface of the trousers and underpants. A similar progressive searching procedure was followed for the women and in both cases the purpose was to save time and to cause the least inconvenience and embarrassment in locating lice when present. The search was discontinued as soon as viable eggs or parasites were found; otherwise it was carried to completion.

It is recognized that examination by this method does not invariably disclose lice when present and that this error always tends to increase the number reported as negative. Nevertheless, more complete examinations would not have been practical under the field conditions obtaining at Imues and Yacuanquer. The work was conducted carefully, however, and it is felt that the results approximate those which would have been obtained had more complete examination been practicable.

The preceding difficulties, of course, do not apply to the head-lice infestation rates since in this case complete examinations were made.

The results in Imues and Yacuanquer indicate that it is practicable and relatively inexpensive by periodic use of DDT and phenyl cellosolve to maintain the louse-infestation index of an entire community at a level sufficiently low to preclude typhus outbreaks and to reduce the incidence of the disease to a position of minor public health importance. They indicate that careful applications of these insecticides at intervals of 4 months to at least 98 percent of the population should maintain the louse-infestation rate at or below 5 percent.

Long continuation of such a program should inevitably result in reaching at least occasionally the small groups missed during the present study. Although it is felt that the periodic mass treatments should be given by well-trained teams which would work necessarily from community to community in a regional control program, supplementary local interim treatment of those missed and of newcomers could well be administered by the priest, the mayor, or a schoolteacher. As the confidence of the people in the harmlessness and effectiveness of the treatment develops they should become more cooperative in not missing treatments, particularly as they come to understand more fully that omissions may result in reinfestation of themselves and of those around them. Then, too, when the control program is carried out on a regional basis the danger of reinfestation from new arrivals and transients (much intercommunity marketing is done) in a given community is much reduced.

Although from a priori reasoning it is evident that low louse-infestation rates bear a direct relationship to the incidence of louse-borne typhus in regions in which the disease is endemic, it would be very difficult except by careful epidemiological studies covering many years, and perhaps not even then, to determine at what level of louse infestation the danger of typhus transmission becomes

negligible or of minor public health importance. Lacking such information it would appear that the adoption of some practicable relatively low louse-infestation index as a criterion of the effectiveness of delousing programs is desirable. On the basis of these experiments it is felt that a 5-percent louse-infestation rate represents a reasonable upper limit to set as the objective, pending the accumulation of information that this standard is too lenient or too severe for the control of louse-born typhus fever as it occurs in primitive communities in Latin America. (Am. J. Hyg., May '48 - J. A. Montoya and P. P. Osejo)

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Compound Fractures in the Navy and Marine Corps: During the years from 1942 through 1945, there were 12,867 cases of compound fractures reported in the Navy and Marine Corps, with an average annual rate of 129.1 per 100,000 strength. When compared with the incidence of simple fractures, it was observed that the ratio in the Navy and Marine Corps was approximately 1 compound fracture to 8 simple fractures. Although the highest incidence of simple fractures occurred in bones of the lower extremity, the highest incidence of compound fractures involved bones of the upper extremity, accounting for 36.9 percent of the incidence. Compound fractures of bones of the lower extremity and bones of the head ranked next highest in incidence.

The average number of sick days per case for total compound fractures was 69.3 as against an average of 42.7 for all the simple fractures. There was a variation in the number of sick days per case for compound fractures from a minimum of 13.4 for compound fractures of the nasal bone to a maximum of 212.3 for compound fractures of the tibia and fibula. The highest average number of sick days per case, 121.6 was for bones of the lower extremity in general.

The lowest average number of sick days per case for compound fractures, 38.4, was reported for compound fractures of bones of the head. This low figure may be due in part to the greater percentage of deaths in this group, since the patients generally died shortly after the condition was incurred. This is particularly true of compound fractures of bones of the skull; for this group there was an average number of sick days per case of 31.5 and a fatality rate of 64.8 per 100 cases.

In comparing compound fractures with simple fractures, one of the most important factors is the difference in the fatality rate. Of the simple fractures, only 0.8 percent terminated in death as compared with a fatality rate of 8.1 for all the compound fractures. Skull fractures, both simple and compound, were notable for their high fatality rates; compound fractures of the skull, however, were almost twice as likely to result in death as simple fractures of the skull, (64.8 percent as against 35.4 percent).

As is true of the simple fractures, invalidings from the Service for compound fractures were also rather infrequent, 2.8 percent of the patients being invalided as compared to 1.5 percent invalided for the simple fractures. Patients with compound fractures of bones of the lower extremity were the most frequently invalided. Of the specific bones, the highest rate of invaliding from the Service because of compound fractures, namely, 11.9 percent, occurred in compound fractures involving the tibia and fibula. (Statistics of Navy Medicine, July '48)

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Osteomyelitis in the Navy and Marine Corps: Diseases of the motor system (Class XVI) rank high in the Navy and Marine Corps in incidence and as a cause of sick days and invalidings from the Service. The highest number of sick days per case among the diseases of the motor system has consistently been caused by osteomyelitis. Data for this disease have been assembled from the Fa-Card (Individual Statistical Report of Patient) for the 10-year period from 1936 through 1945. The incidence is based upon those cases taken up as A (New Admission), ACD and AD (Admitted Contributory Disability and Additional Diagnosis) and EPTE (Existed Prior to Entry into the Naval Service).

During this 10-year period there were 3,901 cases of osteomyelitis in the Navy and Marine Corps. The average annual incidence rate was 35.3 per 100,000 average strength. In addition to these 3,901 cases, there were 551 readmissions.

During the war years there was an average annual incidence rate of 35.9 per 100,000 strength for osteomyelitis as compared to an average annual incidence rate of 30.6 for the 4-year period, from 1936 through 1939. It might have been expected, in view of the increased hazards during the war years resulting in very large numbers of fractures and wounds, that the incidence rate for osteomyelitis would have increased very sharply. That such a slight increase occurred is possibly a reflection of improved methods of treatment. The incidence rates for the entire 10-year period varied from a low of 24.1 in 1939 to a high of 38.2 in 1942.

The EPTE (Existed Prior to Entry) cases, which were a negligible percentage of the total in the prewar years, increased during the war period; in 1942, 33.9 percent of the cases were deemed to have existed prior to the individual's entry into the Service. For the period from 1936 through 1939, an average of only 4.8 percent of the cases were EPTE's as compared to an average of 17.6 percent for the war years.

Data were available for the period from 1937 through 1945 on the diagnoses antecedent to osteomyelitis. During this period 1,254 cases of osteomyelitis were reported as ACD's (Admitted Contributory Disabilities). Compound fracture was the principal diagnosis preceding osteomyelitis; cellulitis, simple

fracture, and gunshot wounds ranked next in that order. Compound and simple fractures combined accounted for 39.0 percent of the diagnoses preceding osteomyelitis, and all types of wounds combined accounted for 24.4 percent. During the years from 1937 through 1945 there was a total of 14,364 compound fractures reported in the Navy; osteomyelitis developed in 330, or 2.3 percent of them. In contrast to this, osteomyelitis developed in only 0.1 percent of the cases of simple fracture and of gunshot wounds.

The data on distribution of the incidence of osteomyelitis by anatomic location was available for the years from 1939 through 1945 in which period there were 3,770 cases of the disease. The specific bones most frequently affected were those of the hand or wrist, which accounted for 26.6 percent of the total. The highest number of cases, 43.0 percent, however, occurred in the lower extremities.

As was previously mentioned, there were 551 readmissions during the 10-year period. It was noted that the percentage of recurrences varied from 12.5 in 1939 to 23.7 in 1944 with an average of 20.5 percent for the 10 years combined. In other words, out of each 5 persons with osteomyelitis sent to duty, it may be expected that 1 will subsequently be readmitted to the sick list for the same diagnosis. During the war years an average of 21,0 percent of those returned to duty was subsequently readmitted as compared to 16.8 percent for the period from 1936 through 1939. Preliminary data for 1946 indicate a new low for readmissions of only 11.7 percent of those returned to duty.

In the early years of the 10-year period a large majority of the patients was returned to duty. However, there was a gradual decline in the percentage returned to duty. Preliminary data for 1946 show a still further decline from 53.9 percent in 1945 to 44.3 percent in 1946. In relation to this decline there was a steady increase during the period in the percentage of patients invalided from the Service. For the four years from 1936 through 1939, an average of only 1.5 percent of the patients was invalided from the Service as compared with an average of 15.9 percent during the war years.

There was a decline in the average number of sick days per case and the noneffective ratios per 100,000 average strength for osteomyelitis in the first half of the period (with the exception of the sick days in 1939) followed by an increase in the later years. In 1945 there was an average of approximately 10 persons out of each 100,000 continually on the sick list with osteomyelitis. Preliminary data for 1946 indicate an increase to approximately 17. This rise has been associated with an increase in the average number of sick days per case, from 103 in 1945 to 122 in 1946.

For the years from 1937 through 1945 there were 241 complications reported. "Deformity, acquired," was the most frequent complication of osteomyelitis, occurring in 48.2 percent of the cases. (Statistics of Navy Medicine, July '48)

Deaths in the Navy and Marine Corps:- 1946: The data in this report concern noncombat-incurred deaths and are compiled from the NavMed N, Certificate of Death.

During the year 1946, with the rapid demobilization and approach to the peacetime strength of the Naval forces, the annual death rate for personnel in the Navy and Marine Corps was 200.9 per 100,000 average strength. This figure represents a decrease of 6.3 percent from the corresponding rate in 1945 and is 29.8 percent below the median rate for the 9 prewar years from 1931 through 1939, which are considered to reflect normal peacetime statistics. The improvement in the rate over that for 1945 was due mainly to the reduction in deaths from injury. However, injuries still accounted for almost two and one-half times as many deaths as were attributed to disease causes.

Noncombat deaths totalling 2,663 were reported in 1946 for personnel of the Navy and Marine Corps on active duty. Among the disease classes, diseases of the circulatory system (Class II) which were responsible for the greatest number of deaths during 1945 ranked second to tumors (Class XXIII) in numerical importance in 1946. Thrombosis of the coronary arteries was again the leading single cause of death among the diseases, with far-advanced active pulmonary tuberculosis and carcinoma ranking next in order. The mortality rate for injuries decreased 13.9 percent from its 1945 level, and the rate for poisonings decreased 12.2 percent during the same period. The leading cause of deaths from injury was multiple extreme injuries; the next most prevalent cause was drowning.

Although the death rate for officers decreased 28.7 percent from the 1945 rate, it was still considerably higher than the death rate for enlisted men. The higher median age for the officer population (29.2 years for officers as against 21.6 for enlisted personnel) may account in part for their higher death rate, the majority of the deaths for circulatory system diseases and malignant neoplasms occurring in the older age groups.

With the exception of tuberculosis, the death rates for white personnel were generally higher than those for Negroes. This confirms previous studies which indicated much higher fatality rates for tuberculosis in Negroes than in white persons. Of a total of 59 deaths for diseases among Negroes, 42 or 71.2 percent were due to tuberculosis (Class XI).

An occupational breakdown showed the highest specific death rates among Marine Corps officers, as a group, with Navy Line officers next in order. For enlisted men the highest rates occurred among the aviation and engine room groups. The large number of deaths among Marine Corps officers as a group and Navy Line officers are attributable in part to the fact that aviation personnel are included in these groups.

The median age at death in 1946, 23.2, was slightly lower than the median of 23.7 in 1945 but one year higher than the median age of all persons in the Navy and Marine Corps. The age specific death rates for Marine Corps enlisted men were higher in all age groups than those of the Navy enlisted personnel.

Mortality data by location of original admission to the sick list indicated that 52.0 percent of the total deaths occurred in Naval activities of the continental United States, 20.1 percent in non-continental areas, and 27.9 percent on ships. The death rate for personnel aboard ship increased 83.3 percent over the corresponding rate in 1945.

From data on mortality caused by violence, the highest rate was for vehicular accidents. This rate, 50.1, which surpasses that of aircraft accidents for the first time since the beginning of World War II, is more than twice as high as the corresponding figure in 1945. For aircraft accidents, far higher death rates occurred among officers than among the enlisted men. This cause of injury was responsible for 70.8 percent of all the deaths attributed to violence among officers.

Age is probably the most significant factor apparent in the mortality experience for diseases of the heart and malignant neoplasms, which, as far as Navy experience in 1946 is concerned, may be designated as diseases of older age groups. (Statistics of Navy Medicine, July '48)

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Moving Averages in Medical Statistics: In the analysis of time series trends, when there are numerous random fluctuations, it is of value occasionally to use a moving average of a series of intervals instead of the individual interval figures. Frequently, these random fluctuations over short periods of time are traceable to very small frequencies and obscure the long-term trend. This, for example, may be the case in observing the fluctuation of the incidence of a disease from month to month, although the general trend over a period of a year, or several years, may be either upward or downward. The effect of averaging the data is to give a smoother curve, lessening the influence of the variations that tend to draw the individual figures away from the general trend. For example, the method of computing a 3-month moving average of a series of monthly figures beginning with January is to add the data for January, February, and March and divide by 3. The average obtained should be posted beside the second month of the series, February. For the next moving average, data for February, March, and April should be used, and the average obtained posted beside the month of March. This procedure (dropping 1 month and adding 1 month) continues until the series is completed.

In the above case, the selection of a 3-month period for the moving average was an arbitrary one. The moving average may be computed for any period of time, depending upon various factors. The longer the period of time included in the average, the smoother the curve secured. This is due to the fact that

the larger the number of items used in obtaining the average, the less important, relatively, becomes any item which is added or dropped. However, the longer the period of time used for the average, the greater the number of values at either end of the series which cannot be computed on the same basis. Random fluctuations from month to month are usually smoothed out by a 3-month moving average. Seasonal fluctuations, however, require a 12-month moving average.

In addition to the use of simple moving averages, statisticians also use weighted moving averages, wherein smoother results may be obtained. In computing a weighted moving average for 3 months, for example, when the middle figure is to be weighted by 2, the procedure is to add the first and third figures, and twice the second figure and divide the total obtained by 4. Thus, the series is weighted at the center. The greater smoothness of the weighted moving average lies in the fact that an item exerts slight influence on the final average when it is first included, but gradually increases in importance and then, as gradually, decreases in importance until it finally disappears. (Statistics of Navy Medicine, July '48)

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Roentgen Therapy and Cancer of the Esophagus and Gastric Cardia: Cancer of the esophagus is of more frequent occurrence than all malignant tumors of bone and is even more common than cancers of the lip, tongue, larynx, or kidney. Carcinoma of the esophagus resembles the intra-oral group of cancers more than it does the gastro-intestinal cancers of glandular origin; the resemblance is evident in three ways: (1) the epidermoid carcinoma is the common histologic type; (2) the age and sex distribution are strikingly similar; (3) there is a common etiologic relationship to chronic irritants, and because of the increasing knowledge of these factors, carcinoma of the esophagus may become one of the preventable cancers.

The medical profession as a whole has had a justifiable pessimism concerning the treatment of esophageal cancer, for the end results have been discouraging. The explanation of this point of view may be found in the following:

1. The obscurity of symptoms renders the diagnosis usually late.

2. The esophagoscope is used infrequently. Only a small minority of patients with symptoms referable to the gullet or cardiac end of the stomach are subjected to early endoscopic examination of the esophagus. There are relatively few physicians trained and equipped for esophagoscopy, certainly not one for every community which can support a hospital. (For the past 15 years every interne, assistant resident, and Fellow of the Memorial Hospital has become proficient in esophagoscopy, bronchoscopy, and gastroscopy; the technic is only slightly more complicated than sigmoidoscopy. The esophagoscopies and bronchoscopies are done on ambulatory outpatients under local anesthesia and the manipulation can be done by a single operator, unassisted.)

3. The esophageal wall is perforated by the carcinoma not infrequently at an early stage in its development, although suppurative mediastinitis and fistulous communication with other viscera may not occur until much later. The esophagus does not have the serosal coat which serves as such an efficient barrier to perforation in the organs of the lower gastro-intestinal system.

4. Esophageal carcinoma is usually highly malignant, a statement that is contrary to many recorded opinions. Metastases often occur early and widely, to a far greater extent than would be expected from epidermoid cancers of their histologic grade of malignancy. It extends intramurally up and down the esophagus for surprising lengths, sometimes far beyond the palpable margins of the tumor; the operator is sometimes profoundly shocked to learn that the pathologist has discovered cancer cells at the very level of transsection. Esophageal cancers tend early to invade contiguous organs within the chest. During the performance of the transthoracic resection with anastomosis, the surgeon frequently discovers that the epidermoid carcinomas of the esophagus have extended greatly below the diaphragm to involve the stomach, the juxta-cardiac lymph nodes, and even the liver. A review of necropsy findings following death from cancers of the esophagus shows impressively the widespread extent of the metastases, even to distant sites.

5. The tumor is often inoperable at the time the diagnosis is established due to the degree of local invasion, the presence of regional and distant metastases, and the poor general condition of the patient.

6. The patient with esophageal cancer is not always a fit subject for radical treatment, surgical or otherwise. He is often elderly, with tissue changes that go along with aging. Malnutrition is another important factor inasmuch as the esophagus is an essential organ of the gastro-intestinal tract and its functional incapacity leads to early inanition. Coexistent pulmonary complications, such as emphysema, bronchitis, tracheal or bronchial fistula, bronchiectasis, tend to handicap surgical intervention.

7. The technic of transthoracic esophagocardiectomy with intrathoracic anastomosis involves grave physiologic and anatomic problems as well as requiring skill, judgment, resourcefulness, special equipment, and well-trained assistance. Because of improvements constantly being made, the operation will undoubtedly be more generally employed in the future.

8. Radiation therapy of esophageal cancers, as it has been employed in the United States, has given only palliative end results. Intracavitary radium therapy using heavily filtered tubes of radium, arranged in tandem formation, has been successful in disengaging the esophageal lumen with improvement in deglutition, but has not completely sterilized these cancers. The radium tandem has been inserted as an intubating applicator, often under fluoroscopic and esophagoscopic guidance, with or without a supplementary gastrostomy. Even when it is perfectly applied and the dose administered with meticulous exactitude, the results are beneficial, but not curative. There are three common reasons for

this failure of radium therapy, namely, (1) impossible adequate distribution of dosage throughout the tumor from such a source, (2) necrosis and sloughing of the infected tumor because of its solution by radium therapy and the consequent occurrence of suppurative mediastinitis, and (3) failure of a linear local source of radiation to reach the distant sites of extension of the cancer. Gold radon seeds used interstitially are also palliative, but fail of cure for the same previously mentioned reasons, to which should be added the extra hazard of their caustic action.

Roentgen therapy of esophageal cancers has been used sporadically in the United States with confirmatory evidence of palliative relief. Sufficient regression of the cancers has occurred, avoiding the necessity for gastrostomy in many instances; swallowing is improved, weight is gained, symptoms disappear, and postradiation x-ray studies have often shown complete or nearly complete disappearance of the tumor. The direct esophagoscopic view corroborates the clinical and radiographic evidence of regression of the cancer following roentgen therapy. The million volt x-ray apparatus has been the most satisfactory modality, using a target-skin distance of 70 cm., a half-value layer of 3.8 cm. of lead, four rectangular ports (two parasternal and two paravertebral), treatment to one port daily of 300 r, and alternating on successive days until a total skin dose of 3000 r x 4 has been administered. The cause of ultimate failure in these patients has occasionally been not local recurrence but distant metastases, which is the same explanation for many surgical failures.

Dr. Jens Nielsen, Chief of the Radium Center in Copenhagen, Denmark, by the application of original and scientific methods has made the most important contributions to the field of roentgen therapy in esophageal cancer. The following principles are direct expressions of his work. Although the idea of rotatory irradiation is comparatively old, being mentioned by Kohl in 1906 and suggested by Pohl in 1913, it has been only during the recent postwar years that it has been developed on a scientific basis by Nielsen. The principle of rotation radiation therapy is to rotate the patient about an axis through the tumor at right angles to the x-ray beam, or vice versa, to rotate the x-ray tube around the stationary patient. It is Nielsen's contention that cancers of the esophagus are especially suitable for rotation roentgen therapy, because the esophagus is situated in an almost central location in the longitudinal axis of the thorax, and these cancers, both by direct extension and lymphatic dissemination, spread in the same axial direction.

The patient is placed on a motor-driven rotating stool, which is turned at a uniform rate, that is, one complete turn in from 10 to 30 minutes, depending on the plan of the therapist. The distance from the x-ray target to the focusing diaphragm is 20 cm., and the distance from the focus to the axis of rotation, that is, the esophageal cancer, is an additional 50 cm. or a total of 70 cm. target-tumor distance. The size of the skin portals are from 4 by 6 to 6 by 10 cm., averaging from 30 to 35 sq. cm. A current of 6 ma. and a potential of 180 kv. are commonly used. The filtration varies from a half-value layer (H.V.L.) of 0.32 mm. cu. (118 cases), to an H.V.L. of 0.9 mm. cu. (56 cases). The stool on which the patient sits is so located that the esophagus lies in the axis of the stool's rotation, which positioning is secured and

maintained by fluoroscopic control. The patient is given a mouthful of a thick barium mixture to swallow and the centering of the x-ray beam is done on this opaque objective, which of course localizes the esophageal cancer. During the entire exposure to treatment, that is, while the patient is being rotated, the observer, who is outside the treatment room, watches this shadow on the fluoroscopic screen interposed between the patient and the lead glass window for the therapist. If the esophageal cancer should fall without the direct beam of radiation, the operator can recenter it by moving the diaphragm of the x-ray machine from one side to the other by means of remote control via a Bowden cable.

By this rotation method a circular band of skin around the chest is irradiated and tanned. Nielsen considered this method as similar to the employment of many small fields which are irradiated in succession, each with a fraction (from a fifteenth to a twentieth) of the full dose. The result of this method of roentgen therapy is that the skin and normal thoracic organs receive a relatively small amount of radiation, but conversely, the esophageal cancer receives an enormous dose because of the constant centering of the beam where it should be. This method takes full advantage of the differential sensitivities of normal and cancerous tissues to radiation therapy and fulfills as far as possible the primary tenet of successful irradiation, namely, to spare the normal tissues, while destroying the cancer.

Nielsen found the most suitable daily dosage to be a tumor dose of from 100 to 200 r (usually 150 r) given in two daily sittings. The total dose into the substance of the tumor is consummated in the course of from 5 to 6 weeks. The bodily effect of these treatments is only a mild degree of radiation sickness characterized by slight nausea, anorexia, leucopenia, fatigue, lowered blood pressure, and loss of weight.

In only 8 of Nielsen's patients was it deemed unwise to administer this treatment. In 34 patients the treatment was solely for palliative purposes. In 140 patients an attempt at curative roentgen therapy was made using the rotation method; 96 of these patients received more than 4000 r into the substance of these esophageal cancers. In four fifths of Nielsen's patients who received the full dose, complete or nearly complete immediate freedom from symptoms was obtained. The patients could swallow and there was radiographic evidence of improvement. Death was due to metastases and cachexia, but the majority of patients were able to swallow until the fatal day. The survival curve for months and years revealed that with rotation roentgen therapy, 25 percent of the patients as against a former 10 percent were alive at the end of one year, and 15 percent as against a former 4 percent were alive at the end of two years.

The technic of roentgen therapy of esophageal cancers, epitomized here, and the end results given represent the best that can be accomplished in the world today by methods other than surgical removal. Nielsen and other Scandinavian radiologists are frankly skeptical that esophagectomy can compete with radiation therapy as a means of affording the greatest relief to the largest number of patients and for the longest time. (Surgery, June '48 - G. T. Pack)

Op24B/cj, Serial 251P24 4 June 1948

To: All Ships and Stations

Subj: Establishment of U. S. Naval Medical Research Unit No. 4

1. The following activity is hereby established, under an officer of the Medical Corps entitled "Officer in Charge":

U. S. Naval Medical Research Unit No. 4
Naval Training Center
Great Lakes, Illinois 4188-475

This activity is under the military command of the Commanding Officer, U. S. Naval Administrative Command, Naval Training Center, Great Lakes, Illinois, and is under the management control of the Bureau of Medicine and Surgery.

2. Bureaus and offices concerned take necessary action.

--SecNav. John L. Sullivan

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BUMED CIRCULAR LETTER 48-73 24 June 1948

To: All Ships and Stations

Subj: Medical Stores; Requisitioning, Receipt Procedures, and Establishment of Stock Levels for

Refs: (a) BuMed Circular Letter 45-23.
(b) BuMed Circular Letter 47-33.
(c) BuMed Circular Letter 47-87.
(d) BuMed Circular Letter 47-109.
(e) BuMed Circular Letter 48-16.
(f) BuMed Circular Letter 44-18.
(g) BuMed Circular Letter 47-60.
(h) BuMed Circular Letter 48-1.
(i) BuMed Circular Letter 48-24.
(j) Article 1906, U.S.N.R.
(k) Par. 23101, BuSandA Manual.

Encls: 1 (HW) Preparation and Submission of BuMed Material Requisition NAVMED-4.
2 (HW) Procedures to be Employed by Continental Shore Facilities in Requisitioning Non-Standard Medical and Dental Supplies and Equipment.

Encls: 3 (HW) Stock Levels of Medical Stores.
4 (HW) Procedures for Receipt of Medical and Dental Supplies and Equipment direct from contractor.

1. References (a) through (e) are hereby cancelled and superseded by enclosures 1, 2, 3, and 4, effective 1 July 1948. Careful scrutiny and study should be given the above enclosures as many new procedures are made effective thereby.

--BuMed. C. A. Swanson

NOTE: Copies of the enclosures which constitute about 18 pages are contained in the 30 June 1948 issue of the Navy Department Bulletin.

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BUMED CIRCULAR LETTER 48-74 29 June 1948

To: NavHosps; NavDisps; MarCorps Activities.

Subj: Optometry and Optical Services

Encl: 1. (HW) Questionnaire to be completed and returned to Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

This letter requests that addressees furnish the Bureau with certain information which will be used in evaluating the present status of optometry and optical services so that plans may be developed to insure the best possible optometrical support of medical services.

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BUMED CIRCULAR LETTER 48-75 7 July 1948

To: Distribution List

Subj: U. S. Naval Medical Material Office, Brooklyn, N. Y.; Mission of

1. The U. S. Naval Medical Material Office, Brooklyn, N. Y., has been established, and shall perform the following functions in accordance with the management and technical directives of the Bureau of Medicine and Surgery, Materiel Division.

(a) Perform Medical Department supply and related functions, including:

(1) Develop medical and dental material allowance lists and revisions thereof for naval vessels, stations, and special activities; and recommend establishment and modification of activity stock levels of medical and dental materials.

(2) Develop data pertaining to cataloging and specifications of medical and dental material.

(b) Prepare detailed estimates of medical and dental material requirements for the operation of Medical Department facilities, based on policies established by the Materiel Division.

(c) Prepare periodic Supply-Demand reviews of medical and dental material as required by effective management practices.

(d) Initiate procurement of medical and dental material based on Supply-Demand reviews.

(e) Assist in the preparation and correlation of data required to support budgetary estimates of the Medical and Dental Stores Program.

(f) Maintain stock and inventory control of medical and dental material at all primary distribution points, and control of distribution of such material to, from, and between these points.

(g) Maintain books of account for receipts, expenditures and balances of medical and dental material of all elements of the Medical Department Supply System.

(h) Develop and promulgate to elements of the Medical Department Supply System Instructions for stock control and reporting, and for the receipt, inspection, stowage, preservation, assembly, issue, distribution, salvage, and repair of medical and dental material.

(i) Maintain plant account records for all Medical Department activities.

(j) Perform such additional accounting functions as may be designated by COMTHREE with concurrence of the Chief of the Bureau of Medicine and Surgery.

--BuMed. C. A. Swanson

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